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EXAMINER	
GAMETT, DANIEL C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,856	TUR ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *1-19,41-52 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-40,53-55 and 57-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/31/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of claims 20, 21, 23-35, 37-40, 53-69, 71, and 72 in the reply filed on 06/17/2009 is acknowledged. The traversal is on the ground(s) that restriction is not proper or required in this case. Applicants assert that the examiner has not afforded applicants a "broad, practical consideration of the degree of interdependence of the alternatives presented" as required according to MPEP § 1850.

2. This is not found persuasive for the following reasons. As stated in the previous office action, the Examiner relies on the PCT International Search and Preliminary Examination Guidelines, Section 10.30, Example 10. The Example is reproduced here:

> 10.30 *Example 10*
> *Claim 1: Conveyor belt with feature A.*
> *Claim 2: Conveyor belt with feature B.*
> *Claim 3: Conveyor belt with features A + B.*
> *Feature A is a special technical feature and feature B is another unrelated special technical feature.*
> Unity exists between claims 1 and 3 or between claims 2 and 3, but not between claims 1 and 2.

3. In the present case, "sequence has been altered so as to improve the free energy of the monomer or of the multimeric complex relative to the wild-type unmutated monomer component so as to be **more stable than the wild-type**, unaltered cytokine protein" (Group I) is analogous to "Feature A". Similarly, "one or more amino acids are substituted for replacement residues so as to provide an **increase in binding affinity and selectivity/specificity** of the cytokine protein" (Group II) is analogous to "Feature B". These features are distinct and unrelated. Stability and selectivity are distinct properties. The instant claims recite non-overlapping sets of amino acid substitutions associated with each of these properties. Therefore, the inventions of Groups I and

II are not obvious variants of one another, they would raise separate issues of patentability, and they would require separate searches of the prior art. Groups I and II are patentably distinct, and restriction between these groups is proper and necessary. Group IV includes a product that combines the features of Groups I and II, analogous to claim 3 in the example. The products of Group IV may be viewed as species with a genus recited in either of Groups I or II.

4. Applicants further argue that the claims of Groups II and III are unified by the recitation of "selectivity." This is persuasive. Therefore, the requirement for restriction between Groups II and III set forth in the office action mailed 04/17/2009 is hereby withdrawn. This further necessitates consideration of Group V, claims 37 and 70, as unity exists between these claims and Group III.

5. It is noted that claim 56 recites dependency from claim 52. Therefore, claim 56 properly belongs to Group I. This does not alter the subject matter of the groups or the propriety of the restriction requirement. Therefore, claim 56 will be withdrawn from consideration along with the claims of Group I. If desired, Applicants may re-introduce claim 56 into the elected group by amending its dependency.

6. The remainder of the restriction requirement is still deemed proper and is therefore made FINAL.

7. Claims 1-19, 41-52 and 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/17/2009.

8. Claims 20-40, 53-55, and 57-72 are under consideration.

Specification

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. The application is not in compliance with 37 CFR 1.821(c), which requires that Patent applications which contain disclosures of nucleotide and/or amino acid sequences must contain, as a separate part of the disclosure, a paper or compact disc copy (see § 1.52(e)) disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper or compact disc copy is referred to elsewhere in this subpart as the "Sequence Listing.", and 37 CFR 1.821(e), which requires that a copy of the "Sequence Listing" referred to in paragraph (c) of this section must also be submitted in computer readable form (CRF) in accordance with the requirements of § 1.824.

10. Applicant is given a period concurrent with the period for response to this office action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Applicant is referred to MPEP 2401-2431 for information regarding compliance with sequence rules.

Claim Objections

11. Claim 34 objected to because of the following informalities: Apparent typographical error: "D21E8F". Appropriate correction is required. For purposes of examination, the claim is interpreted as reciting "D218F".

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 23, 26-34, 39, 40, 55, 60, 61, 67-69, and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite mutations at one or more numbered positions in "the cytokine" of their respective base claims. The independent claims, however, do not recite a single cytokine but rather recite a genus of β-sheet multimeric cytokines. Other base claims recite "TRAIL", which does not denote a species, as it would apply equally to orthologous proteins from any animal. Therefore, the antecedent basis for "the cytokine" is unclear. Furthermore, the meaning of recited amino acid positions is unclear given that no specific reference sequence is recited and multiple cytokines are contemplated.

14. Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 71 recites the limitation "cytokine according to claim 53". The antecedent

basis for this limitation is unclear. Claim 53 is drawn to a method, not at product. A "cytokine according to claim 53" could be a cytokine from the beginning or end, or at any step of the method.

15. Claims 65 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 65 and 66 provide for the use of TRAIL variants, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

16. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

17. Claims 65 and 66 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 35-38 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. Independent claims 36 and 36 are drawn to a genus of β-sheet multimeric cytokines with altered amino acid sequences that cause the cytokine to both be more stable and to have enhanced stability and increased binding affinity and selectivity/specificity for the target receptor, relative to the wild-type cytokine. The dependent claims narrow the genus of cytokine to members of the TNF ligand family (claims 37 and 70) or to TRAIL (claim 38). The TNF ligand family includes at least 16 members listed in Table 6 of the instant specification. The TNF ligand family is presented as a subgenus within the genus of β-sheet multimeric cytokines. It is not clear how much larger the genus of β-sheet multimeric cytokines is, as compared to the subgenus of the TNF ligand family; the specification asserts that additional examples in the larger genus will be known to those of skill in the art ([0025] in the published application). The term "TRAIL" does not denote a species, as it would apply equally to orthologous proteins from any animal. Therefore, the claims encompass a large genus of molecules that differ from a large genus of known molecules in ways that are described only by a desired functional outcome. That is, the claimed cytokines are defined not by what they are, but what they do.

21. "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed… Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

22. Only two species within this genus are fully defined structurally: a TRAIL cytokine which differs from the human TRAIL of SEQ ID NO:1 by the presence of mutations D269H and T214R or the presence of mutations D269H, E194I and I196S. With the exception these two species, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. While "examples explicitly covering the full scope of the claim language" typically will not be required, a sufficient number of representative species must be included "to demonstrate that the patentee possessed the full scope of the [claimed] invention." Lizardtech, Inc. v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

23. Therefore, a TRAIL cytokine which differs from the human TRAIL of SEQ ID NO:1 by the presence of mutations D269H and T214R or the presence of mutations D269H, E194I and I196S, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

25. Claims 20-28, 33, 54, 55, 57-60, 63-69, 71, and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 2004/001009 (Hymowitz), filed June 23, 2003, with a claim of priority to June 24, 2002 (of record). The instant claims are drawn to a cytokine product defined broadly by functional properties and specifically by the presence of mutations at one or more amino acid positions. The recited positions are interpreted as referring to the human TRAIL polypeptide of SEQ ID NO:1. Hymowitz discloses human TRAIL which is mutated at positions 191, 267, and

269, including D269R (Table III, p. 74). Hymowitz, therefore, discloses TRAIL mutants that are indistinguishable from those specifically recited in instant claims 23, 28, 55, 60, 67, 69, and 72, and generically recited in the remaining claims. The courts have established that if a claimed product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir.1983).

26. Citing the work of others, Hymowitz teaches that Apo2L/TRAIL, alone or in combination with chemotherapy or radiation therapy, can exert substantial anti-tumor effects (p. 3, lines 15-19). Consequently, Hymowitz teaches administration of the disclosed Apo2L/TRAIL variants in conjunction with other forms of therapy, including radiation therapy, cytotoxic agents, and chemotherapeutic agents (claim 36, paragraph bridging pp. 52-53). Also citing earlier work, Hymowitz teaches that it was well known in the art that Apo2L/TRAIL induces apoptosis in cancer cells through "death receptors" DR4 and DR5, and not through other TRAIL receptors and decoy receptors (p.6, line 1 to p. 7, line 9). These teachings anticipate instant claims 63-66, as far as the claims are understood.

27. Claim 20-27, 54, 55, 57-59, 67, and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/00832 (Ashkenazi; of record), published January 4, 2001. The instant claims are drawn to a cytokine product defined broadly by functional properties and specifically by the presence of mutations at one or more amino acid positions. The recited positions are interpreted as referring to the human TRAIL polypeptide of SEQ ID NO:1. Ashkenazi discloses

human TRAIL which is mutated at positions 130, 149, 155, 191, 195, 218, 267, and 269 (Table 1, p.22; Example 4, p. 24). Ashkenazi, therefore, discloses TRAIL mutants that are indistinguishable from those specifically recited in instant claims 23, 55, and 67, and generically recited in the remaining claims. The courts have established that if a claimed product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir.1983). While identical products inherently have all of the same properties, it is noteworthy that Ashkenazi recognized that certain of the recited mutations would result in decreased affinity for DR4 and DcR2, and therefore, selectivity for DR5 as recited in instant claims 22, 26,27, 58, and 59 (see paragraph bridging pp.24-25).

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 53 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20040146968 (Chung), filed January 10, 2001.

30. Claims 53 and 62 are drawn to methods for obtaining variants of a β-sheet multimeric cytokine with increased binding affinity and selectivity/specificity for a target receptor (both

claims) and enhanced stability (claim 62). With regard to affinity and selectivity/specificity, the claims recite steps of identifying amino acid residues that interact with receptor, eliminating from consideration amino acids that interact with conserved receptor residues or the receptor backbone, and substituting the remaining candidate residues with amino acids that include side-chain conformations that are predicted to fit into the binding interface with the target receptor.

31. Chung discloses a three-dimensional structure of a TRAIL-sDR5 complex, which is taught to be useful in molecular strategy for regulating TRAIL stability, and the specificity, and affinity of binding between TNF-related cytokines and their receptors (see Abstract). Chung teaches that stability can be altered by changing amino acids in the homotrimer or homodimer interfaces [0106-0107]. Chung teaches that mutants with changed receptor binding affinity receptor are easily constructed by using the major amino acids of the receptor binding site [0108]. Thus, Chung suggests the general methods recited in claims 53 and 62.

32. Chung did not explicitly state that alteration of amino acids that interact with conserved receptor residues or the receptor backbone should be avoided when mutating TRAIL to increase stability and/or increased binding affinity and selectivity/specificity for a target receptor, as recited in instant claim 53 c) and 62 b). However, these limitations would be understood by one of skill in the art to be implicit in the suggestion to engineer TRAIL with desired useful properties. Furthermore, these considerations are supported by the disclosed results. Chung et al., assert that the disclosed crystal structure identifies previously unappreciated contacts between residues 131-135 of TRAIL and sDR5. The three interacting residues of sDR5 are identical or homologous substituted in the other three TRAIL receptors [0149]. Chung then constructed a deletion mutant for residues 131-135 and found that it has drastically reduced

binding affinity and biological activity ([0154-1060]; Fig. 5). While this was taken by Chung et al. as confirmation of the model, it also illustrates the obviousness of avoiding alteration of amino acids that interact with conserved receptor residues, if one is attempting to design a useful cytokine. One of skill in the art would expect that interaction with conserved residues is critical for binding and, therefore, alteration of these interactions should be detrimental to binding. This was confirmed by the Chung results. Furthermore, if the object is selectivity, it would only be logical to target interactions that are specific to each receptor, not those which are conserved among all receptors.

33. Therefore, the plan for obtaining cytokine variants recited in the instant claims differs from the general suggestions put forth in Chung only by reciting particular considerations that would be understood by one of skill in the art to be implicit in, or logical extensions of, the teachings in Chung. Therefore, the instant claims are *prima facie* obvious in view of Chung.

Conclusion

34. No claim is allowed.

35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 20070161564 is an equivalent disclosure to WO 01/00832. US 6740739 is the US National Stage entry of WO 9936535, of record. US 20060141561 is the US National Stage entry of WO 2004/001009, of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647